

Bruce Narloch, Ph.D.  
Toxicologist  
CHEVRON ENVIRONMENTAL  
HEALTH CENTER  
15299 San Pablo Avenue  
Richmond, CA 94804-0054  
(415) 231-6144

Robert A. Neal, Ph.D.  
Center in Molecular Toxicology  
Department of Biochemistry  
VANDERBILT UNIVERSITY  
School of Medicine  
Nashville, TN 37232  
(615) 343-6572

Dr. D. Newkirk  
Department of Health and Human  
Services  
Center for Veterinary Medicine  
U.S. FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane (HFV-142)  
Rockville, MD 20857

Dr. Thomas S. Osdene  
Vice President  
Science and Technology  
PHILIP MORRIS USA  
P.O. Box 26603  
Richmond, VA 23261  
(804) 274-2692

Robert E. Osterberg, Ph.D.  
Supervisory Pharmacologist  
Center for Drug Evaluation  
and Research  
U.S. FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane  
Rockville, MD 20857  
(301) 443-4300

Dr. Paula F. Paul  
Manager, Regulatory Affairs  
NORAM CHEMICAL COMPANY  
3509 Silverside Road  
Wilmington, DE 19803  
(302) 575-2050

Dr. Joe Pedelty  
HOLCOMB ENVIRONMENTAL SERVICES  
17375 Garfield Road  
Olivet, MI 49076  
(616) 763-9442

Waldir Pedersoli  
Pharmacologist  
Center for Veterinary Medicine  
U.S. FOOD AND DRUG ADMINISTRATION  
Agricultural Research Center  
Center Road, Building 328A  
Beltsville, MD 20705  
(301) 344-2556

Emil Poulsen, D.V.M., Ph.D.  
Chief Advisor in Toxicology  
MINISTRY OF HEALTH  
19, Moerkhoej Bygade  
DK-2860, Soeborg  
Denmark  
(01) 696600

\*Paul R. Portney  
Vice President  
RESOURCES FOR THE FUTURE  
1616 P Street, NW  
Washington, DC 20036  
(202) 328-5093

Mary L. Quaife, Ph.D.  
Chemistry/Toxicology Consultant  
1506 33rd Street, NW  
Washington, DC 20007  
(202) 333-8391

Richard E. Quellette, Ph.D.  
Manager, Toxicology  
HOECHST CELANESE CORPORATION  
P.O. Box 2500  
163 BedI  
Sommerville, NJ 08876

Mark J. Reasor, Ph.D.  
Department of Pharmacology  
and Toxicology  
WEST VIRGINIA UNIVERSITY  
Morgantown, WV 26505  
(304) 292-2418

<p>A. K. Reddy, Ph.D.            Manager, Product Safety &amp;            Regulatory Compliance            THE CLOROX COMPANY            7200 Johnson Drive            Pleasanton, CA 94566            (415) 847-6280</p> <p>Ralph C. Reynolds            Manager, Health Issues            Health and Environment Laboratories            EASTMAN KODAK COMPANY            Kodak Park - B320            Rochester, NY 14652-3615            (716) 588-3978</p> <p>Esther Rinde, Ph.D.            Toxicologist            U.S. ENVIRONMENTAL PROTECTION AGENCY            401 M Street, SW (H7509C)            Washington, DC 20460</p> <p>Dr. Ann E. Robinson            Science Policy Adviser            Occupational and Environmental            Health and Safety            ONTARIO MINISTRY OF LABOUR            14th Floor            400 University Avenue            Toronto, Ontario M7A 1T7            Canada            (416) 326-7582</p> <p>*Richard J. Ronk            Director, Product Policy Staff            Center for Food Safety and            Applied Nutrition            U.S. FOOD AND DRUG ADMINISTRATION            200 C Street, SW (HFF-4)            Washington, DC 20204            (202) 472-5676</p> <p>Randy N. Roth            Manager, Toxicology            ARCO CHEMICAL COMPANY            P.O. Box 2679-TA            Los Angeles, CA 90051            (213) 486-8733</p>	<p>Mr. Louis Rothschild            Editor            FOOD CHEMICAL NEWS            1101 Pennsylvania Avenue, SE            Washington, DC 20003            (202) 544-1980</p> <p>Dr. Alan M. Rulis            Chief, Regulatory Food Chemistry            Branch (HFF-414)            U.S. FOOD AND DRUG ADMINISTRATION            200 C Street, SW            Washington, DC 20204            (202) 485-0321</p> <p>*Dr. Lesley Russell            Professional Staff            Committee on Energy and Commerce            U.S. HOUSE OF REPRESENTATIVES            2125 Rayburn House Office Building            Washington, DC 20515            (202) 225-2927</p> <p>*Professor Ragnar Rylander            Department of Environmental Hygiene            UNIVERSITY OF GOTHENBURG            Box 33031            S-400 33 Gothenburg            Sweden            (031) 85 36 01</p> <p>*Dale P. Sandler, Ph.D.            Epidemiologist            NATIONAL INSTITUTE OF ENVIRONMENTAL            HEALTH SCIENCES            P.O. Box 12233, MD A305            Research Triangle Park, NC 27709            (919) 541-4668</p> <p>Dr. L. Saslaw            Department of Health and Human            Services            Center for Veterinary Medicine            U.S. FOOD AND DRUG ADMINISTRATION            5600 Fishers Lane (HFV-154)            Rockville, MD 20857</p>
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Manfred Schach von Whittenau, Ph.D.  
Vice President, Safety Evaluation  
PFIZER INC.  
Eastern Point Road  
Groton, CT 06340  
(203) 441-4851

Mary Schackelford, Ph.D.  
General and Molecular Toxicology  
Branch  
U.S. FOOD AND DRUG ADMINISTRATION  
200 C Street, S.W.  
Washington, DC 20204  
(202) 245-1077

Dr. L. Schechtman  
Department of Health and Human  
Services  
Center for Veterinary Medicine  
U.S. FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane (HFV-154)  
Rockville, MD 20857

\*Robert J. Scheuplein, Ph.D.  
Acting Director  
Office of Toxicological  
Sciences, CFSAN  
U.S. FOOD AND DRUG ADMINISTRATION  
200 C Street, SW  
Washington, DC 20204  
(202) 485-0046

Jean Pierre Schied, D.V.M.  
ROUSSEL UCLAF  
163 Avenue Gambetta  
75020 Paris  
France  
4797-0539

Dr. Kenneth R. Schrankel  
Director, Flavor and Fragrance  
Safety Assurance  
INTERNATIONAL FLAVORS &  
FRAGRANCES INC.  
1515 Highway 36  
Union Beach, NJ 07735  
(201) 888-2305

\*Fred R. Shank, Ph.D.  
Director  
Center for Food Safety and  
Applied Nutrition  
U.S. FOOD AND DRUG ADMINISTRATION  
200 C Street, SW  
Washington, DC 20204

\*Philippe Shubik, D.M., D.Phil.  
President  
TOXICOLOGY FORUM, INC.  
Suite 800  
1575 Eye Street, NW  
Washington, DC 20005  
(202) 659-0030

Dr. Jarnail Singh  
Professor of Environmental  
Toxicology  
STILLMAN COLLEGE  
3600 15th Street  
P.O. Box 1430  
Tuscaloosa, AL 35403  
(205) 349-4241 ext. 605

Dr. R. B. Singh  
Senior Medical Officer  
Toxicology & Environmental Health  
Division  
UNITED KINGDOM DEPARTMENT OF HEALTH  
Room 910, Hannibal House  
Elephant & Castle  
London SE1 6TE  
United Kingdom  
1-972-2150

Dr. Agam Sinha  
Statistician Principal  
AMERICAN CYANAMID COMPANY  
Clarksville Road  
Princeton, NJ 08543  
(609) 799-0400

Jerry M. Smith  
Director, Corporate Toxicology  
ROHM AND HAAS  
Independence Mall West  
Philadelphia, PA 19105  
(215) 592-2986

Emmanuel Somers, Ph.D.  
Drugs Directorate  
Health Protection Branch  
HEALTH AND WELFARE CANADA  
Tunney's Pasture  
Ottawa, Ontario  
Canada K1A 0L2  
(613) 957-0369

Arpad Somogyi, Ph.D.  
Max von Pettenkofer Institute  
BUNDESGESUNDHEITSAMT  
Thielallee 88-92  
D-1000 Berlin 33  
Federal Republic of Germany  
(49) 30 8308-2446 or 2447

James W. Stanley, Ph.D.  
Vice President  
Scientific and Regulatory Affairs  
PEPSICO, INC.  
100 Stevens Avenue  
Valhalla, NY 10595  
(914) 742-4531

Richard H. Stanton  
Regulatory Affairs Manager  
VALENT USA  
Suite 405  
1700 K Street, NW  
Washington, DC 20006  
(202) 872-4681

\*Dr. Thomas B. Starr  
Principal  
ENVIRON  
Suite 300  
4350 N. Fairfax Drive  
Arlington, VA 22203

Donald E. Stevenson  
Consultant, Toxicology  
HEALTH, SAFETY & ENVIRONMENT  
P.O. Box 4320  
Houston, TX 77210  
(713) 241-0032

Connie J. Stone, Ph.D., J.D.  
Manager, Life Sciences  
THE COCA-COLA COMPANY  
P.O. Drawer 1734  
Atlanta, GA 30301  
(404) 676-2121

Dr. Fred H. Stults  
Vice President, Product Safety  
& Regulatory Affairs  
FIRMENICH INCORPORATED  
P.O. Box 5880  
Princeton, NJ 08543  
(609) 452-1000, Ext. 355

Dr. Robert L. Suber  
Manager, Scientific Affairs  
RJR NABISCO, INC.  
Bowman Gray Technical Center  
Reynolds Boulevard  
Winston-Salem, NC 27102  
(919) 741-5544

Dr. Thomas Sulkowski  
Department of Health and Human  
Services  
Center for Veterinary Medicine  
U.S. FOOD AND DRUG ADMINISTRATION  
5600 Fishers Lane (HFV-144)  
Rockville, MD 20857

\*James A. Swenberg, D.V.M., Ph.D.  
Visiting Professor  
UNIVERSITY OF NORTH CAROLINA  
Department of Pathology  
Campus Box 7095  
Chapel Hill, NC 27599

\*Michael R. Taylor, Esq.  
KING & SPALDING  
1730 Pennsylvania Avenue, N.W.  
12th Floor  
Washington, DC 20006  
(202) 737-0500

Martin Terry, D.V.M., Ph.D.  
Director, Scientific Activities  
ANIMAL HEALTH INSTITUTE  
P.O. Box 1417  
Alexandria, VA 22313-1480  
(703) 684-0011

Kay Thomas  
Issue Analyst  
THE TOBACCO INSTITUTE  
1875 Eye Street, NW  
Washington, DC 20006  
(202) 457-4800

Sara Thurin  
BNA CHEMICAL REGULATION REPORTER  
1231 25th Street, NW  
Washington, DC 20037  
(202) 452-4584

Keith C. Triebwasser, Ph.D.  
Associate Director  
THE PROCTER & GAMBLE COMPANY  
6071 Center Hill Road  
Cincinnati, OH 45224  
(513) 634-6967

\*Angelo Turturo, Ph.D.  
Assistant to the Director  
NATIONAL CENTER FOR TOXICOLOGICAL  
RESEARCH  
NCTR Drive HFT-1  
Jefferson, AR 72079  
(501) 541-4014

B. Frank Vincent, Ph.D.  
Associate Director, Regulatory  
Compliance  
JAMES RIVER CORPORATION  
1915 Marathon Avenue  
Neenah, WI 54956  
(414) 729-8152

Dr. Thomas A. Vollmuth  
Senior Toxicologist  
LORILLARD TOBACCO CO.  
420 English Street  
P.O. Box 21688  
Greensboro, NC 27420  
(919) 373-6663

Dr. Roger Walk  
Toxicologist  
INBIFO  
Fuggerstrasse 3  
D-5000 Koln  
Federal Republic of Germany

R. Herbert Wallick  
Manager, Chemical and  
Analytical Research  
LIGGETT GROUP INC.  
Research Department  
P.O. Box 1572  
Durham, NC 27702  
(919) 683-9324

Karen C. Warner  
SHOOK, HARDY & BACON  
1200 Main  
One Kansas City Place  
Kansas City, MO 64105  
(816) 474-6550

Dr. Michael D. Waters  
Director, Genetic Toxicology  
Division, HERL  
U.S. ENVIRONMENTAL PROTECTION  
AGENCY (MD-68)  
Research Triangle Park, NC 27711  
(919) 541-2537

Michael Watson  
Pesticide Safety Division  
Harpenden Laboratory  
MINISTRY OF AGRICULTURE,  
FISHERIES AND FOOD  
Matching Green, Harpenden  
Hertfordshire AL5 2BD  
United Kingdom  
(582) 715241 ext. 2261

A. Judson Wells  
Special Assistant, Smoking and  
Health  
AMERICAN LUNG ASSOCIATION  
41 Windermere Way  
Kennett Square, PA 19348  
(215) 388-1045

\*Dr. Lawrence M. Wexler  
Director Epidemio Group  
NEW YORK MEDICAL COLLEGE  
One Lincoln Plaza, 18D  
New York, NY 10023  
(212) 787-1703

Donald K. Weymouth  
Director, Animal Science Projects  
Management and Animal Products  
Regulatory Services  
ELI LILLY AND COMPANY  
P. O. Box 708  
Greenfield, IN 46140  
(317) 277-4465

Vivian A. Williams  
Toxicologist  
U.S. ENVIRONMENTAL PROTECTION AGENCY  
401 M Street, SW  
Washington, DC 20460

Dr. James D. Wilson  
Vice President  
AMERICAN INDUSTRIAL HEALTH COUNCIL  
1330 Connecticut Avenue, NW  
Washington, DC 20036  
(202) 659-0060

\*Jeanette Wiltse  
National Air Toxics Coordinator  
Office of Air and Radiation  
U.S. ENVIRONMENTAL PROTECTION AGENCY  
401 M Street, SW (ANR 443)  
Washington, DC 20460  
(202) 382-7403

\*Dwain L. Winters  
Policy Director, Office of  
Toxic Substances  
U.S. ENVIRONMENTAL PROTECTION AGENCY  
401 M Street, SW  
Washington, DC 20460  
(202) 382-6907

\*Dr. Gerhard Zbinden  
Professor of Toxicology  
Institute of Toxicology  
SWISS FEDERAL INSTITUTE  
OF TECHNOLOGY  
Schorenstrasse 16  
CH-8603 Schwerzenbach  
Switzerland  
41-1-825-1010

\*Lauren Zeise, Ph.D.  
CALIFORNIA DEPARTMENT OF HEALTH  
State of California  
2151 Berkeley Way  
Berkeley, CA 94704  
(415) 540-3221

DR. WITORSCH: Thank you, Dr. Gori.

(Slide) What I am going to try to cover in the limited time available are some of the non-neoplastic respiratory effects of environmental tobacco smoke exposure. So, it will be a little bit of a change of pace. Now, studies of the respiratory effects of non-neoplastic respiratory effects of ETS have been basically of two types. They have included epidemiologic studies of chronic or long-term exposure addressing either pulmonary function from the point of view of spirometry or respiratory symptoms or disease, and studies of this type have been done both in adults and in children.

There have, also, been experimental studies of acute exposure where individuals are exposed in exposure chambers to defined amounts of environmental tobacco smoke, and these studies have been done in normal subjects, as well as in asthmatic subjects. In the interests of time, I am going to limit my remarks during the presentation to the epidemiologic studies in adults, and we can certainly get into some of the other areas, if there is time during the discussion period.

Now, there have been through the end of 1989, 15 epidemiologic or epidemiologic-like studies of ETS exposure in adults that have looked at, as end points, either pulmonary function test parameters or respiratory symptoms or both (Slide) and as you can see, some of the studies have looked at both, and some have looked at one or the other.

You can, also, see, those of you who can read the slide, and I apologize for to those who cannot that these studies have been done really in a variety of geographic areas within the United States, in different parts, as well as in other countries throughout the world, so that there is a pretty fair distribution in terms of cultural and geographical factors.

Many of the studies have used spousal smoking as the index or surrogate of ETS exposure. Many others have used household smoking which, of course, in most cases or in many cases, at least, include spousal smoking as the index of ETS exposure, and only a few studies have looked at anything that involved occupational work exposure.

None of these studies published to date has looked at any other kind of index of ETS exposure, and none of them has addressed any of the biological markers that Dr. Haley spoke about earlier, and none of them has addressed any other kind of environmental marker, so that we are really talking about surrogate indices of ETS exposure for the most part involving spousal smoking or some household smoking that, also, includes spousal smoking, and I think that is important to keep in the studies in context (Slide) because reliance on spousal smoking or an index including spousal smoking as an index of ETS exposure subjects these studies, any epidemiologic study to certain problems, and these are similar, virtually the same problems that characterize the studies of lung cancer that were mentioned, and I will just briefly mention, and that includes exposure misclassification which for the most part represents or introduces a non-differential bias and smoking status misclassification which introduces a differential bias, and this differential bias in part relates to marital aggregation or concordance, namely the phenomenon that smokers tend to marry smokers and non-smokers tend to marry non-smokers, so that you are more likely to have misclassified smokers among the spouses of smokers than you are to have it among the spouses of non-smokers, and there are, also, some particular confounding variables that have been alluded to and addressed earlier that relate to life style, socioeconomic and other kinds of factors that married couples tend to have in common.

Now, bias from misclassified ex-smokers as I mentioned is more likely (Slide) in studies relying on spousal smoking index, and this is a differential bias. It is particularly more likely where the classification is by current smoking status, that is where studies only address the subject's current smoking status. It is more likely that you will have a problem with ex-smokers, former smokers who are currently non-smokers who are misclassified or regarded as never smokers, and in the studies of non-neoplastic respiratory effects, in contrast to many of the studies of lung cancer, many more of the non-neoplastic studies have only looked at current smoking status.

That is important in the studies addressing respiratory function or pulmonary function because the effects of active smoking on pulmonary function include both reversible and irreversible effects, and while it is true that when individuals stop smoking their pulmonary function may improve, it doesn't all improve, and it doesn't completely improve, and when one looks at groups of individuals, large groups of individuals, one finds generally as a reasonable generalization that the pulmonary function of ex-smokers is somewhere intermediate between that of the pulmonary function of active smokers and that of the pulmonary function of never smokers, and that becomes important when looking at the data.

(Slide) Just to briefly mention, and this was really addressed to some extent in Dr. Rylander's talk and has been addressed in some of the comments that there are a number of variables that may affect respiratory function, that may affect respiratory health and that may be shared by married couples that could influence the results of epidemiologic studies, such things as alcohol consumption, transmissible infection, health habits and attitudes, life style and so on.

Of the studies that were done through the end of 1989, 12 of the studies (Slide) looked at pulmonary function as an end point, and they are listed here. These studies for the most part were studies relying on spousal smoking or household smoking as the index of ETS exposure.

Now, these studies looked at a variety of spirometric parameters as measures of pulmonary function, but basically they were either FEV1, the forced expiratory volume in 1 second or some variant thereof or some analogous parameter on the one hand or FEF2575, forced expiratory flow 2575, the rate of flow during the middle half of the forced vital capacity maneuver or some analogous parameter or variant thereof, and it is important to note the difference between those parameters.

The FEV1 is sort of a tried and true test that has been used for many years, is very useful, is very useful in field studies. It is reasonably reproducible. It correlates very well with pulmonary dysfunction and pulmonary disease. It has one problem. It is somewhat insensitive and will not pick up some degrees of dysfunction.

The FEF2575, on the other hand, is much more sensitive than the FEV1. In fact, unfortunately, it is too sensitive, and it is a test that has a wide inter-individual variability and a particularly wide intra-individual variability, with a very high coefficient of variation, and for that reason reductions in FEF2575 are difficult to interpret, and there is a lot of uncertainty about the clinical, physiological and pathological correlation of reductions, even abnormalities, let alone reductions within the normal range of that and related parameters, and while it has been suggested that FEF2575 may be an index of small airway disease, disease limited to the bronchioles, less than 2 to 3 millimeters in diameter, that is far from generally accepted and is, in fact, a matter of considerable controversy and uncertainty.



There are clearly individuals who have abnormal FEF2575 who have no demonstrable dysfunction otherwise or disease, and there are individuals who have normal FEF2575 who do have significant air flow obstruction, so that it is a difficult parameter to rely on.

Now, of the results of the 12 studies which are listed here, and there are two results that are not listed on the slide which I just want to point out. Just for orientation, the arrow, the horizontal arrow represents no change. ND refers to the test was not done and an arrow pointing downward refers to a reduction in that parameter.

(Slide) In addition to the data indicated here, the Kauffman et al study in 1983, while finding no overall abnormalities did report reductions in FEV1 and FEF2575 in a subgroup of their subjects, namely women over the age of 40 years, and the Salem et al study in 1984, while reporting no abnormalities or no reductions in the standard parameters studied did report a reduction in air velocity index and a prolongation in expiratory time, parameters that are of uncertain significance, but should be mentioned, at least for completeness.

If one includes the studies as positives studies or studies showing the change, overall of the 12 studies, in seven there was some reduction in a test or more of pulmonary function in individuals said to be exposed to ETS using the index of ETS exposure used compared to individuals said not to be exposed to ETS.

On the other hand, in five of the 12 studies there were no significant differences. Those findings really don't permit any meaningful conclusion about the effects of ETS exposure on pulmonary function. I think there is too much variability, variation in the studies to allow one to reach any meaningful conclusion, just on the surface.

Furthermore, there are problems with those studies. We mentioned the problems of the index of ETS exposure, misclassification and confounding variables which really characterize all of the studies (Slide) both those purporting to show an effect, as well as those purporting to show no effect.

In many of the studies or some of the studies, at least, the differences noted were limited to FEF2575 and related parameters, and the significance of reductions in that parameter and related parameters is really uncertain.

Where differences were noted, in virtually all cases, they were small, generally in the range of 3 to 15 percent reductions and most of the reductions less than 5 percent, and all of the values were generally within the normal range.

Finally, there were internal inconsistencies in some, some implausible results like inverse dose response relationships, as well as questions about the methodology, design, instrumentation, about some of the studies that just adds to the difficulty and uncertainty with regard to reaching any conclusions.

(Slide) Eight studies looked at respiratory symptoms, and some of these eight studies are the same ones that looked at pulmonary function, and all of these studies relied on spousal or household smoking as an index of ETS exposure, and among these eight studies without reading all of this to you, four of them showed no increased incidence of symptoms associated with ETS exposure, while the other four reported some increase in respiratory symptoms associated with ETS

exposure, again, a variation that doesn't permit any conclusion, and the same kinds of problems (Slide) characterized those studies as characterized the studies of pulmonary function.

(Slide) So, what can we say about the studies of effects of ETS on respiratory function or respiratory disease or chronic ETS exposure in adults? To summarize the studies with pulmonary function, even liberally interpreting the data, 7 of 12 showed some decrement in PFT parameters, but 5 of 12 showed no decrement of PFT parameters.

Studies of respiratory symptoms or disease, 4 of 8 an increased frequency, 4 of 8 no increased frequency. I think in the context of all of the problems with the studies but even outside of that context these results are too variable to permit any conclusion of association and the answer, I think remains to be determined in this particular area.

Thank you.

## STUDIES OF THE RESPIRATORY EFFECTS OF ETS

### EPIDEMIOLOGIC STUDIES OF CHRONIC EXPOSURE

- PULMONARY FUNCTION (SPIROMETRY)
- RESPIRATORY SYMPTOMS OR DISEASE

### EXPERIMENTAL STUDIES OF ACUTE EXPOSURE

- NORMAL SUBJECTS
- ASTHMATIC SUBJECTS

SPOUSAL SMOKING AS INDEX OF ETS EXPOSURE

SES - RELATED VARIABLES

EXPOSURE MISCLASSIFICATION

- NON-DIFFERENTIAL BIAS

SMOKING STATUS MISCLASSIFICATION

- DIFFERENTIAL BIAS
- MARITAL AGGREGATION

CONFOUNDING VARIABLES

- LIFESTYLE

ALCOHOL CONSUMPTION

INCOME

EDUCATION

HOUSING/LIVING SPACE

OCCUPATION

ETHNICITY

TRANSMISSABLE INFECTIONS

HEATING & COOKING

TRANSPORTATION

LIFESTYLE

HEALTH HABITS/ATTITUDES

DIET

BIAS FROM MISCLASSIFIED EX-SMOKERS

MORE LIKELY IN STUDIES RELYING ON SPOUSAL SMOKING INDEX

DIFFERENTIAL BIAS

MORE LIKELY WHERE CLASSIFIED BY CURRENT SMOKING

SMOKING EFFECTS BOTH REVERSIBLE AND IRREVERSIBLE

TABLE 1. EPIDEMIOLOGIC STUDIES OF ETS EXPOSURE IN ADULTS:  
PULMONARY FUNCTION AND RESPIRATORY SYMPTOMS

Study	Source of Subjects	Index of ETS Exposure	Endpoints Measured
Schilling et al., 1977	3 U.S. Communities	Spousal smoking	PFT parameters Respiratory symptoms
Simecek, 1980	Czechoslovakia	Spousal smoking	Respiratory symptoms
White and Froeb, 1980	California	Exposure at work > 20 yr	PFT parameters
Comstock et al., 1981	Maryland	Household smokers	PFT parameters Respiratory symptoms
Kauffmann et al., 1983	France	Household smokers	PFT parameters
Lebowitz, 1984	Arizona	Household smokers	PFT parameters Respiratory symptoms
Gillis et al., 1984	Scotland	Household smokers	Respiratory symptoms
Salem et al., 1984	Egypt	Home and work	PFT parameters
Kentner et al., 1984 and 1988	Germany	Current ETS exp.	PFT parameters
Brunekeef et al., 1985	Netherlands	> 10 cig/d smoked in the home	PFT parameters
Hosein and Corey, 1986	3 U.S. communities	Household smokers	PFT parameters
Kalandidi et al., 1987	Greece	Spousal smoking	Diagnosis of COPD
Svensen et al., 1987	18 U.S. cities	Spousal smoking	PFT parameters
Kauffman et al., 1989	France <sup>a</sup> 5 U.S. cities	Spousal smoking	PFT parameters Respiratory symptoms
Hole et al., 1989 <sup>b</sup>	Scotland	Household smokers	PFT parameters Respiratory symptoms

<sup>a</sup>Same study population reported in Kauffman et al., 1983

<sup>b</sup>Same study population reported in Gillis et al., 1984

# EPIDEMIOLOGIC STUDIES OF ETS AND PULMONARY FUNCTION IN ADULTS

Study	Source of Subjects	Index of ETS Exposure
Schilling et al., 1977	3 U.S. Communities	Spousal smoking
White and Froeb, 1980	California	Exposure at work > 20 yr
Comstock et al., 1981	Maryland	Household smokers
Kaufmann et al., 1983	France	Household smokers
Lebowitz, 1984	Arizona	Household smokers
Salem et al., 1984	Egypt	Home and work
Kentner et al., 1984 and 1988	Germany	Current ETS exposure
Brunekeef et al., 1985	Netherlands	> 10 cig/d smoked in the home
Hosein and Corey, 1986	3 U.S. communities	Household smokers
Svendsen et al., 1987	18 U.S. cities	Spousal smoking
Kauffman et al., 1989	France and U.S.	Spousal smoking
Hole et al., 1989	Scotland	Household smokers

## SPIROMETRIC PARAMETERS

FEV<sub>1</sub>

- REASONABLY REPRODUCIBLE
- SOMEWHAT INSENSITIVE
- CORRELATES RELIABLY WITH DYSFUNCTION/DISEASE

FEF<sub>25-75</sub>

- WIDE INTER-INDIVIDUAL VARIABILITY
- WIDE INTRA-INDIVIDUAL VARIABILITY
- UNCERTAIN CLIN/PHYSIOL/PATHOL CORRELATIONS

TABLE 2. EPIDEMIOLOGIC STUDIES OF ETS EXPOSURE AND PULMONARY FUNCTION IN ADULTS

Study	Reported Change in Parameter				
	FEV <sub>1</sub>	FVC	FEF <sub>25-75</sub>	PEF	MEF <sub>75</sub>
Schilling et al., 1977	-	-	nd	nd	nd
White and Froeb, 1980	-	-	↓	nd	nd
Comstock et al., 1981	-	-	nd	nd	nd
Kauffmann et al., 1983	-	-	-	nd	nd
Salem et al., 1984	-	nr	-	-	nd
Lebowitz, 1984	nd	nd	nd	-	nd
Kentner, 1984 and 1988	-	-	-	↓	↓
Brunekreef et al., 1985	-	-	nd	↓	↓
Hosein and Corey, 1986	-	nd	nd	nd	nd
Svensen et al., 1987	↓	nd	nd	nd	nd
Kauffmann et al., 1989	-	-	nd	nd	nd
Hole et al., 1989	↓	nd	nd	nd	nd

# EPIDEMIOLOGIC STUDIES-USING PFT PARAMETERS

## PROBLEMS

INDEX OF ETS EXPOSURE, MISCLASSIFICATION, CONFOUNDING VARIABLES

DIFFERENCES LIMITED TO FEF, . . . , AND RELATED PARAMETERS

SMALL DIFFERENCES, VALUES GENERALLY WITHIN NORMAL RANGE

INTERNALLY INCONSISTENT, IMPLAUSIBLE DATA

METHODOLOGY, STATISTICS, DESIGN AND INSTRUMENTATION

### EPIDEMIOLOGIC STUDIES OF ETS AND RESPIRATORY SYMPTOMS IN ADULTS

<u>Study</u>	<u>Source of Subjects</u>	<u>Index of ETS Exposure</u>
Schilling et al., 1977	3 U.S. Communities	Spousal smoking
Simecek, 1980	Czechoslovakia	Spousal smoking
Comstock et al., 1981	Maryland	Household smokers
Lebowitz, 1984	Arizona	Household smokers
Gillis et al., 1984	Scotland	Household smokers
Kalandidl et al., 1987	Greece	Spousal smoking
Kauffman et al., 1989	France and U.S.	Spousal smoking
Hole et al., 1989	Scotland	Household smokers

EPIDEMIOLOGIC STUDIES OF ETS EXPOSURE AND  
RESPIRATORY SYMPTOMS IN ADULTS

<u>Study</u>	<u>Findings</u>
Schilling et al., 1977	No association with cough, phlegm, wheeze
Simecek, 1980	Increased symptoms of bronchitis
Comstock et al., 1981	No association with cough, phlegm, wheeze
Lebowitz, 1984	No association with cough, rhinitis, wheeze, shortness of breath
Gillis et al., 1984	Increased prevalence of expectoration and hypersecretion in males, and dyspnea in males and females
Kalandidi et al., 1987	Increased risk of COPD
Kauffmann et	No association with cough or phlegm; In U.S. population, increased prevalence of wheezing; In French population, increased prevalence of dyspnea in women $\geq 40$
Hole et al., 1989	No increased risk of expectoration, dyspnea or hypersecretion

EPIDEMIOLOGIC STUDIES USING SYMPTOMS/DISEASE

PROBLEMS

INDEX OF ETS EXPOSURE, MISCLASSIFICATION, CONFOUNDING VARIABLES

INCONSISTENCIES BETWEEN STUDIES

INCONSISTENCIES WITHIN STUDIES

QUESTIONS OF PLAUSIBILITY AND DIAGNOSTIC CRITERIA



EPIDEMIOLOGIC STUDIES OF RESPIRATORY

EFFECTS OF CHRONIC ETS EXPOSURE

- SUMMARY/CONCLUSIONS -

STUDIES OF PULMONARY FUNCTION

- 7 OF 12 : SOME DECREMENT IN PFT PARAMETER(S)
- 5 OF 12 : NO DECREMENT IN PFT PARAMETERS

STUDIES OF RESPIRATORY SYMPTOMS/DISEASE

- 4 OF 8 : INCREASED FREQUENCY
- 4 OF 8 : NO INCREASED FREQUENCY

RESULTS TOO VARIABLE TO PERMIT CONCLUSION OF  
ASSOCIATION

DR. GORI: I have a question, Phil. The problem here of irritation, real or psychogenic, if you wish, what kind of an effect would that have on the respiratory function?

DR. WITORSCH: Irritation, of course, is an acute effect, and certainly a high enough concentration of ETS, environmental tobacco smoke is a potential mucous membrane irritant, and in high enough concentration can certainly lead to irritation.

Studies that have been done in asthmatics, for example, show that a small number of asthmatics may react to exposure to environmental tobacco smoke with an exacerbation of asthma, and various studies somewhere in the range of up to about 20 percent or to look at it the other way, 80 percent apparently don't react.

In some cases, where there are high concentrations of ETS, that is certainly an acute irritant effect. In other cases where the concentrations are not particularly high, that may represent a response to an odor because it is very difficult, as you know, to disguise or mask the odor of tobacco, and it has been well recognized that asthmatics may respond to odor by developing increased bronchospasm. The mechanism of that is unclear. It may represent psychogenic mechanisms or it may represent something else, and finally, we know that asthmatics will respond with increased airway resistance to psychogenic influences.

One can repeatedly induce asthma by suggestion. One can deal with asthma in some patients by hypnosis. One can tell a patient, and these studies have all been done, that this particular substance is something that is going to make you have bronchospasm, and aerosolize saline, and the person will develop bronchospasm.

One can then aerosolize the same thing and tell the patient that this is a bronchodilator, and they will promptly develop bronchodilatation, so that psychogenic factors certainly are important, and that is an area that again, we don't have any definitive answers.

DR. GORI: Dr. Shubik?

DR. SHUBIK: Dr. Witorsch, what kind of findings would you have with asymptomatic smokers using these procedures?

DR. WITORSCH: It depends on how long they have been smoking, and it depends on a number of factors. If you take young people, and from where I stand, that is people up into their thirties, even who have been smoking for 10 to 20 years, perhaps, you may find that a certain percentage of them who are totally asymptomatic, perhaps 20 percent of them may have reductions in midflow rates, FEF<sub>2575</sub>. Some of those individuals may have small airway disease. The majority of them probably don't. Some of those individuals, if they stop smoking, those changes will disappear. Others, if they stop smoking, those changes won't disappear. Some of them, if they continue to smoke, and some of this is anecdotal data, and some of it has actually been looked at. David Bates looked at a large series of individuals. Some of them, if they continue to smoke, their changes will worsen. Others, if they continue to smoke will not develop significant air-flow obstruction. I think what that tells us is that there are a number of variables that are operative in determining which individuals will develop chronic air-flow obstruction related to active smoking, and that probably includes genetic factors, perhaps dietary factors, perhaps other factors.

If you looked at active smokers overall, probably no more than about 15 percent of active smokers develop clinically significant air-flow obstruction or 85 percent of them develop nothing more significant in terms of chronic airway disease than so-called "catarrhal" bronchitis, cough and sputum production, without a significant air-flow obstruction, and that doesn't relate very well to pack years of smoking. So, there are clearly other factors, immunologic, genetic and so on that are involved.

DR. BERNARD: Bernard, Scientific Research Associates. One of the principles that I have always used, whether we are dealing with tobacco smoke or food or pharmaceuticals or what have you is the issue of relative risks.

I think one of the places that our society has gone wrong is that we are looking at every risk as though it has equal importance, pumping in lots of money into things which have relatively little bang for their buck. We would do better to deal up front with the more important risks in terms of priority setting.

From what I have seen here this morning, I am just underwhelmed by the data supporting the relationship between ETS and some effect, and even given the methodological problems of which there are many, one would expect, I think that if this were a significant problem that the data would be perhaps a little more clear-cut.

The conclusion that I come to, based upon what I see here is that whereas the society is moving towards enacting regulations which limit exposure to passive smoking in the workplace, it appears that the data would show that that is not where the risk is, if there is any, that the risk is really in the home, and perhaps what we need to do is start passing laws with regard to smoking in one's home.

DR. WITORSCH: I won't disagree with that comment. Maybe Dr. Gori, as Chairman, would like to say something.

DR. GORI: This is too hot an item. Any other questions for Dr. Witorsch?

Yes?

DR. HOOD: I was just wondering what the relative magnitudes of the effects are that are seen in active smokers that you just discussed versus the ones that have been found or claimed for the ETS-exposed people in the studies that were the main thrust of your talk.

DR. GORI: May I remind you to say your name?

DR. HOOD: Oh, Ron Hood, University of Alabama.

DR. WITORSCH: To say that it is orders of magnitude is probably understating it. I think that if you would look at the quantitative degree of air-flow obstruction, for example, which is an objective parameter that you could measure, you are talking about differences that are many thousands of times different. You are talking about in the case of active smoking where you have clinically significant air-flow obstruction resulting in symptoms and complications and values that are clearly in the abnormal range. When you are talking about the numbers found in ETS exposure where there are decrements, you are talking about numbers that A, stay within the normal range, B,

are on the average about 5 percent or less below what the theoretical normal is for that individual and are not associated with any chronic symptoms that are attributable to them.

DR. LEE: Peter Lee. I will ask you two questions. One, you quoted some studies which showed a decrease, other studies that didn't. Was there any difference between the studies that did and the studies that didn't in general? I mean were the ones that didn't sort of smaller or did some large well-conducted studies show no decrease?

Secondly, with regard to the last speaker, I felt the Calendidi study claimed to show frank COPD from ETS which seems totally contrary to all the rest of the literature, but I would like your thoughts on that one.

DR. WITORSCH: Let me comment on the Calendidi study first. The Calendidi study was reported in 1987, in *Lancet* as a letter to the editor, and they report something like 103 said to be never-smoking women living in Athens who did not have asthma, did not have any other respiratory risk factors, other than being married to a smoking spouse who were said to have, and I use the word intentionally, a chronic obstructive pulmonary disease, so-called "COPD" or for those who are not familiar with it, the chronic bronchitis emphysema syndrome.

There are several problems with that study. The first is that in the format of a letter to the editor, there is not enough data to really evaluate their diagnostic criteria and a number of other factors and unfortunately, I have seen, although I have been looking for it, no follow-up full study published in the literature with that data.

Secondly, it is extremely unique, so unique as to raise questions of plausibility for anyone to encounter 100 cases of chronic obstructive pulmonary disease in a non-smoking population, even in a chest hospital in a 2-year period. It is so unique, and I say this from the point of view of being a pulmonary internist, it is so unique that one seriously has to raise questions about the diagnosis and/or whether in fact, the smoking status classification was accurate, and I think either or both of those could lead to it, but I don't think I have seen 100 cases of COPD in non-smokers in 20 years of practice to say nothing of 2 years and that is in the practice of pulmonary medicine. So, I think that there are serious questions about that.

As to the first question, there are no real differences between the studies. I mean some controlled a little better for confounding variables. Lebowitz, for example, in his studies in Arizona pays more attention to confounding variables even though Lebowitz has said that he thinks that we overemphasize confounding variables. He spends a lot of time on them. His results were negative. On the other hand, there are criticisms of his studies and the exposures of that population. I don't think there is any -- they are all equally good or equally bad. I think until we have at least a questionnaire that is verified with biomarkers, I think it is impractical to have the subjects verified with biomarkers, but it is practical to do a biomarker verification of a questionnaire and then use a questionnaire. Most of these studies did not use standardized, let alone verified questionnaires, and until we get that, we are not going to have a meaningful study.

DR. GORI: Thank you, Dr. Witorsch. It is getting more and more interesting. Our next speaker is Dr. Dale Sandler, trained formally at the Hopkins University and now associated with the branch of epidemiology at the National Institute of Environmental Health Sciences.